II. REMARKS

Upon entry of the amendment, claims 1-38, 40, 50, 55, 60, and 80-82 will be pending. Claims 38, 40, and 50 are amended herein, and claims 80-82 are newly added. A marked-up copy showing the amendment to the specification and the claims is attached hereto as Exhibit A. No new matter is added with the amendments. The amendment to claim 38 and 40 are supported by claims 39 and 40 respectively, as filed. The amendment to claim 50 corrects a typographical error. Newly added claims 80-82 are supported for example, by Example 12.

Claim Rejection under 35 U.S.C. § 112, First Paragraph

Claims 1 to 15, 19 to 28, 31 to 37, and 60 were rejected under 35 U.S.C. § 112, first paragraph as allegedly not enabled by the specification as filed. Applicants respectfully traverse the rejection.

The Office Action alleges that although the specification discloses how the claimed methods can be used *in vitro*, the claims are drawn to methods that encompass transgenic non-human mammals and the state of the art for the production of transgenic animals at the time of filing was allegedly unpredictable. For example, the Office Action asserts that the level and specificity of expression of a transgene as well as the phenotype of a transgenic animal are dependent on the specific transgene construct used, and are species dependent. Therefore, the Examiner concluded that the phenotype of a theoretical transgenic animal was unpredictable at the time of filing. Furthermore, the Examiner clarified that the phenotype referred to in the office action is expression of the destabilized recombinant molecules.

It is the Applicants view that the claims are not directed to methods of producing transgenic organisms, or to the transgenic organisms themselves, but to cells and methods of detecting activity in a cell, regulating protein expression in a cell, or a host cell itself. Even if the cells are considered to part of a transgenic organism, the factors that determine the success and operability of the claimed methods within the cell are defined and predictable, and as admitted in the Office Action fully enabled by the present disclosure. By contrast the factors that determine the ultimate cellular phenotype of an adult transgenic animal are a completely

different set of variables that are irrelevant to the pending claims, because the claims are not directed to this feature, as acknowledged on page 5 line 10 of the current office action.

The present invention utilizes the ubiquitin protein degradation system, which is the major protein degradation system in eukaryotic cells. As such, one of ordinary skill in the art will recognize that the methods can be employed using eukaryotic cells in general, regardless of whether or not the organism from which the cells are derived is transgenic.

It is also noteworthy that unexamined claims 64 and 68, which are directed to transgenic organisms, and represent distinct inventions. Furthermore, newly added claims 80-82 are directed to *in vitro* methods.

In summary, it is submitted that the pending claims are enabled by the disclosure as filed and, therefore, it is respectfully requested that the rejection of the claims under 35 U.S.C. § 112, first paragraph, be removed.

Claim Rejection under 35 U.S.C. § 102

The Office Action rejected claim 38 under 35 U.S.C. § 102(a) as being anticipated by Corish et al. (Protein Engineering 12 (12) 1035-1040 (1999). Applicants traverse the Office Action's rejection of claim 38 under 35 U.S.C 102. Claim 38 has been amended to recite the limitation of claim 39 wherein the destabilization domain includes a ubiquitin homolog. Corish is silent as to the use of a destabilization domain that includes a ubiquitin homolog. Therefore, claim 38 as amended is not anticipated by Corish et al. This conclusion is impliedly conceded by the pending office action which did not reject claim 39 as anticipated by Corish et al. Accordingly, Applicants respectfully request withdrawal of the rejection of claim 38 under 35 U.S.C. § 102(a).

In view of the amendments and the above remarks, it is submitted that the claims are in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

Date: September 23, 2002

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Enclosures: Exhibit A

EXHIBIT A

MARKED-UP COPY OF THE SPECIFICATION AND THE CLAIMS SHOWING THE AMENDMENTS

In the Claims

Please cancel claim 39, without prejudice.

Please amend the claims as follows:

38. (Amended) A method of destabilizing a target protein in a cell, comprising; operatively coupling a target protein to a linear multimerized destabilization domain, wherein said linear multimerized destabilization domain is non-cleavable by a α-NH-ubiquitin protein endoproteases, and comprises at least two copies of a destabilization domain, and wherein said destabilization domain comprises a ubiquitin homolog.

40. (Amended) The method of claim [39] 38, wherein said ubiquitin homolog comprises a mutation that prevents cleavage by α-NH-ubiquitin protein endoproteases.

50. (Amended) A recombinant DNA molecule, comprising a nucleic acid sequence encoding [for];

d) a linear multimerized destabilization domain, wherein said linear multimerized destabilization domain is non-cleavable by [a] α-NH-ubiquitin protein endoproteases, and comprises at least two copies of a destabilization domain,

e) a target protein, and

f) a linker moiety that operatively couples said multimerized destabilization domain to said reporter moiety,

wherein said linker is non-cleavable by a α-NH-ubiquitin protein endoproteases.